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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,484	KOSUGI ET AL.	
	Examiner	Art Unit	
	GAILENE R. GABEL	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 15-29* is/are pending in the application.

4a) Of the above claim(s) *16 and 18-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1 and 15-29* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/14/06; 1/15/08; 3/25/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Amendment Entry

1. Applicant's amendment filed August 25, 2008 was acknowledged and entered. Claims 2-14 were. Claims 15-29 were added. Claims 1 and 15-29 were subjected to a restriction requirement.

Election/Restrictions

2. Applicant's election of Group I, claims 15-22, filed December 22, 2008 is acknowledged and has been entered. Applicant also elected 1) Method Species A which is recited in claim 15 and 2) Source Species A which is recited in claim 17 which is drawn to "a peptide containing a sequence of 5 to 20 amino acid residues selected from the amino acid sequence at positions 90 to 130 of SEQ ID No. 2." Claims 16 and 18-29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected inventions and species. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Accordingly, claims 1 and 15-29 are pending. Claims 1, 15, and 17 are under examination.

Information Disclosure Statement

3. The listing of references in the specification on pages 2-4 is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 15, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in reciting, "a disease related to endometriosis" in the preamble and the last two lines of the claim because it is unclear as to what the disease is, that is related to endometriosis and/or how it relates to endometriosis. The phrase, "related to" is a subjective term that lacks a comparative basis for defining its metes and bounds, i.e. how does the disease relate to endometriosis. The phrase "related to" also renders the claim indefinite because it includes elements not actually disclosed (those encompassed by "diseases related to [endometriosis]"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

Claim 1 is indefinite in reciting, "a normal biological sample" in both first occurrence and second occurrence in the claim because the term "normal" is a relative term that lacks a comparative basis for defining its metes and bounds. Does Applicant perhaps intend that the biological sample has a normal level or range of HRF contained therein?

Claim 1 is indefinite in reciting, "a subject", "a patient", and "a person" because it is unclear as to whether each recitation intends the same "test subject." This rejection can be overcome by using consistent language when referring to the same element in the claim.

Claim 1 is also confusing in reciting, "determining that the subject showing a significantly higher HRF protein level compared with that of the normal biological sample in a patient with a disease related to endometriosis" because its is unclear what Applicant intends to encompass in the term "showing." Perhaps, Applicant intends "having." Additionally, the recitation of "normal biological sample in a patient with a disease" is confusing because it is unclear how a patient with a disease has a normal biological sample." It is unclear as to whether the recitation of the term "determining" intends an actual active positive method step in the claimed method because it appears to recite a mental step instead. Lastly, the phrase "significantly higher" is also indefinite because the phrase reflects subjective and relative terms that lack a comparative basis for defining their metes and bounds; the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 1 is also indefinite in reciting, "determining … "a disease related to endometriosis or a person with high risk thereof" because it fails to clearly define how "the disease" or "high risk thereof" should be differentially diagnosed between each other.

The term "high" in reference to high risk in claim 1 is a relative term which renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Same analogous comments and problems in claim 1 apply to claims 15 in the recitation of "a disease related to endometriosis."

Claim 15, step a) is vague and indefinite in reciting, "contacting a biological sample… with a support on which a first antibody recognizing an HRF protein is immobilized" because it is unclear how the first antibody "recognizes" the HRF protein which appears to be intracellular in nature from within endometrial tissue. Claim 15, step a) therefore, is unclear as to whether the first antibody which "recognizes" the HRF protein actually "binds" to capture the HRF protein.

Claim 15, step b) is indefinite in reciting, "washing the support with which the biological sample has been contacted" because it is unclear what Applicant intends. Specifically, by washing [away] "the support", both those that recognized (and bound???) the HRF protein and the unbound components appear to be washed away in the process. It appears that step b) should recite, "washing the resultant mixture in step

a) to remove unbound components," i.e. unbound support and unbound sample components, so as "to retain the support having the bound/captured HRF protein thereto."

Claim 15, step c) is therefore vague and indefinite in reciting, "contacting a second antibody recognizing a different epitope of HRF protein… with the support in step b)" because it is unclear what the second antibody should interact with if the solid support in step b) is "washed." Claim 15, step c) is also unclear as to how the second antibody should "recognize" the HRF protein which appears to be intracellular in nature from within endometrial tissue. Claim 15, step c) therefore, is unclear as to whether the second antibody which "recognizes" a different epitope of the HRF protein actually "binds" the epitope so as to label the [captured] HRF protein in the solid support.

Claim 15 step d) is confusing and contradictory in reciting, "measuring a … free label on the support" because it is unclear how the label which should be bound by the secondary antibody to the HRF protein on the support, is "free." Please clarify. Does Applicant perhaps intend, "measuring the complex formed by the labeled second antibody with the HRF protein that bound to the first antibody immobilized on the support."

Accordingly, claim 15, step e) lacks clear antecedent basis in reciting, "the label amount measured in the step d) as an indicator of the HRF protein level" because it is unclear what label, i.e. bound or free, is being measured. It is specifically unclear how the free label is an indicator of the HRF protein level if it is not bound on the support by the HRF protein and the first antibody.

Claim 15, step e) also lacks antecedent basis in reciting, "the result of a normal biological sample" since a normal biological sample does not appear to have been assayed or measured.

Claim 15, step f) is also confusing in reciting, "employing a significantly higher HRF protein level compared with that of the normal biological sample as an indicator showing a disease related to endometriosis" because its is unclear what Applicant intends to encompass in the term "showing." Perhaps, Applicant intends "providing indication of…". Additionally, claim 15, step f) fails to clearly define how to "employ" any other HRF protein levels that can be resulted.

Claim 15, step f) is also indefinite in reciting, "a disease related to endometriosis or a person with high risk thereof" because it fails to clearly define how "the disease" or "high risk thereof" should be differentially measured and diagnosed between each other.

Claim 17 lacks clear antecedent basis in reciting, "the antibody is an antibody recognizing an HRF protein" since claim 15 appears to recite a first antibody and a second antibody. Additionally, claim 17 is unclear in relation to claim 15 from which it depends because the first antibody and the second antibody in claim 15 appear to recognize or bind distinct HRF protein epitopes. Therefore, does each of the first antibody and the second antibody recognize and bind distinct epitopes within the peptide containing the 5 to 20 amino acid residues at positions 90-130 of SEQ ID No. 2 in the instant claim?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Oikawa et al., (Increased expression of IgE-dependent histamine-releasing factor in endometriotic implants, Journal of Pathology 199: 318-323 (January 13, 2003)).

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Oikawa et al. teach a method of diagnosing endometriosis by measuring the level of histamine-releasing factor (HRF) protein in a biological sample, i.e. endometrial tissue, of a patient, comparing the level to the concentration of HRF protein in normal endometrial tissue control from individuals not having endometriosis, and the method providing an indication that the patient has endometriosis if the HRF protein level in the patient is significantly increased in comparison to the normal control level of HRF protein (Abstract; p. 319, col. 1; and p. 320, col. 1 and 2) The level of HRF protein is measured using a first antibody (HRF-TPY) that binds to an epitope of HRF protein and a second antibody (HRF-GKL) that binds to another epitope of HRF protein. The antibodies are generated from an immunogen comprising a peptide having a sequence of 5-20 amino acid residues (16 AA residues: GKLEEQRPERVKPFMT) within 90 to 130 amino acid positions (101-116 amino acid positions) of SEQ ID No. 2 (p. 319, col. 2 and p. 322, col. 1). See also Figure 3.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oikawa et al. (Journal of Pathology 199: 318-323 (January 13, 2003)) in view of Hochstrasser et al. (WO 94/12881)).

Oikawa et al. has been discussed supra. Oikawa et al. differ from the instant invention in failing to teach that the first anti-HRF antibody is immobilized to solid support and the second anti-HRF antibody is conjugated to a label.

Hochstrasser et al. teach an immunological method to detect a marker protein designated as Translationally Controlled Tumor Protein p21 (TCTPp21) present in growing cells (Abstract). Immunological methods include fluorescent immunoassays and ELISA. Increase of this marker protein in growing cells provides indication of active cell growth which in cancer conditions, i.e. ovarian cancer cells and cervical cancer cells, is unregulated. Hochstrasser et al. specifically teach generating antibodies specific to TCTPp21 and using these anti-TCTPp21 antibodies to detect TCTPp21 present in the cells. TCTPp21 may also be expected in lymph nodes or body fluid of patients (p. 1 line 9 to p. 2, line 5; and p. 4, lines 24-34). Where cell tissues are obtained, Hochstrasser et al. teach lysing the cells so as to release or expose the TCTPp21 protein and use the lysate in immunoassay to detect the TCTPp21 protein (p. 4, line 35 to p. 5, line 4 and p. 6, lines 14-19). The sample is contacted with a first anti-TCTPp21 antibody that is immobilized to a solid support (ELISA plate) and that binds to an epitope of the TCTPp21 protein. After the plate containing the sample is incubated and then washed, the sample is further contacted to a second anti-TCTPp21 protein antibody that is conjugated to a fluorescent or enzyme label and that binds to another epitope on the TCTPp21 protein to label the protein bound to the solid support. The labeled resulting complex on the support is measured so as to obtain a concentration of the TCTPp21 protein and then compared to normal TCTPp21 protein control levels (p.

12, Example 2). The first antibody and the second antibody may be polyclonal or monoclonal and are generated from TCTPp21 immunogen or peptide fragment thereof which comprises a peptide having a sequence of 5-20 amino acid residues (16 AA residues: GKLEEQRPERVKPFMT) within 1-41 amino acid positions of TCTPp21 protein.

In as far as the histamine-releasing factor or HRF protein (SEQ ID No. 2) and antibodies specific thereto recited in claims 15 and 17, the amino acid residues of TCTP21 immunogen as taught by Hochstrasser et al. in 1-41 AA positions is 100% homologous to the amino acid residues within 90 to 130 AA positions of SEQ ID No. 2 (p. 6, lines 7-13).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to immobilize to a solid support and label with a fluorescent or enzyme label each one of MAb HRF-TPY and MAb HRF-GKL as taught by Oikawa that each binds to different epitopes of the HRF protein so as to immunologically assay HRF protein using the method of Hochstrasser which detects a peptide having the same amino acid residues of TCTPp21 consonant to 90-130 AA positions of the HRF protein of Oikawa, in order to obtain a quantitative measure of the HRF protein in a patient suspected of having endometriosis, because Hochstrasser taught and suggested incorporating antibodies that are specific to the same immunogenic peptide into a solid support and label for use as capture and label antibodies in immunological methods to detect the presence of the peptide in proteins of growing cells. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the

anti-HRF antibodies taught by Oikawa into the solid support and label of immunological assays taught by Hochstrasser to detect and quantitate the same peptide present in HRF proteins because Oikawa found that HRF protein if detected accurately in significantly high concentrations using immunological assays, has a direct correlation with occurrence of endometriosis and taught that the HRF protein is a determinative marker in diagnosis of endometriosis in patients.

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GAILENE R. GABEL whose telephone number is (571)272-0820. The examiner can normally be reached on Monday, Tuesday, Thursday, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

May 15, 2009